REMARKS

With the entry of the present Amendment, claims 47-58 are canceled and new claims 59-71, drafted for improved clarity, are entered in this application. None of the amendments made herein constitutes the addition of new matter. The amendments made herein are believed to place this case in condition for allowance.

The Telephone Interview

Applicants appreciate the time spent by the Examiner in the telephone interview held February 3, 2005.

The rejections under 35 U.S.C. 112, first and second paragraphs, were discussed. The Examiner indicated that the rejections were based on the interpretation of claim 47, as presented in Item 1, page 2, of the Office Action. The discussion of alternative claim language to remove these rejections has been implemented in the claims entered in this Amendment.

The Rejections under 35 U.S.C. 112, first paragraph

Claims 47-52 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, has possession of the claimed invention. Applicants respectfully traverse this rejection.

Applicants have canceled claims 47-58 without prejudice. The new claims presented herein contain language which Applicants believe more clearly defines the steps of the present invention. Applicants remind the Examiner that the rejections made under

Section 112 were based on a particular interpretation of the method of the present invention, which interpretation would not be applicable to the newly entered claims.

The Office action has clarified that the alleged lack of written description is not being applied against the recited specific probes and primer, but only the extract, purified or amplified sample that is only functionally defined ... hybridize with a functionally defined detection means.

It is alleged that the detection means comprises a sequence of any number of nucleotides in length and may be of any sequence that will detect any Plasmodial malarial agent that is known to share some homology (*P. falciparum*) or less homology (*P. vivax*) with *P. berghei* (McCutcheon, 1984). McCutcheon teaches that the human parasite *P. vivax* fits into a different group from that of the human parasite *P. falciparum* and *P. berghei* (a rodent parasite).

Applicants respectfully note that an important and surprising aspect of the present invention is that the noted portion of sequence (nucleotides 1147-1740 of SEQ ID NO:1) is, in fact, uniquely characteristic of the Plasmodium species that parasitize humans. One assay that can detect the various human parasites is a particularly valuable contribution to the art.

It has been alleged that the genus of hybridization reagents utilized in the claimed methods have not been described to reasonably convey that the inventors were in position of the invention at the time the application was filed.

With respect to hybridization reagents in general, Applicants respectfully state the hybridization reagents are well known to those of ordinary skill in the art. With respect to

particular nucleotide sequences characterizing the probes or primers used in the present claimed methods, Applicants have claimed those of at least 15 contiguous nucleotides within SEQ ID NO:1, nucleotides 1147 to 1740. Of necessity, the upper limit is the full extent of nucleotides 1147 to 1740 of SEQ ID NO:1. It should not be necessary to recite each 15 or greater nucleotide sequence within that recited portion of SEQ ID NO:1, but rather stating in "shorthand" should constitute sufficient written description of those sequences, which are so clear to one of ordinary skill in the art. That skilled artisan recognizes from this statement that the inventors were in possession of the invention at the time the application was filed. This is not the same fact pattern as that of the Vas Cath case. With respect to the nucleic acid (if any) within the biological sample, Applicants respectfully state that it is not necessary to define the structure of that nucleic acid in the sample. Where there is detectable hybridization (directly detected or via a polymerase chain or reverse transcriptase polymerase chain reaction amplification product), one concludes that a human Plasmodium parasite was present in the biological sample. Where there is no detectable hybridization (directly detected or via a polymerase chain amplification product), one concludes that a human Plasmodium parasite was not present in the biological sample. There is no concern with other types of nucleic acid present in the sample.

With respect to the statement that claims 47-52 contact a sample that has been extracted, purified or amplified with a detection means, it was alleged that the source of the biological sample is not so claimed to set forth what nucleic acid has been extracted, purified or amplified.

It has been Applicants' intention to cover the situation wherein nucleic acid is extracted, purified or amplified from the biological sample prior to contacting that nucleic acid with a primer or probe specific to a human Plasmodium parasite. It should not be

necessary to recite the source of the biological sample in the claim. If there is a human Plasmodium malarial agent present in the sample, its DNA and/or RNA will have been extracted and will react by hybridizing to the probe (or primer) of the present invention. However, in the interest of advancing prosecution, Applicants present new claim 59, which is believed to clearly recite that the biological sample is from a human or animal that can be infected with a Plasmodium human malarial agent.

In Paragraph 6, the Patent Office states that the genus of claimed methods that utilize any nucleic acids that have been extracted, purified or amplified and only functionally defined to hybridize with any functionally defined detection means have not been so described in the specification. The Examiner has noted that there is a highly variable genus of nucleic acid molecules ... teaches populations "exhibit high levels of genetic polymorphism present in Plasmodial malarial agents.

Applicants respectfully submit that the very heart of the invention and Applicants' important contribution to the art is the recognition of a sequence (nucleotides 1147-1740, or a sequence of at least 15 contiguous nucleotides thereof) which is characteristic of the human malarial parasites and that this characteristic sequence (or a portion thereof) can be used to detect the presence of human malarial parasites in a biological sample containing same (it is understood that if these parasites are not there, detection is negative). It is the surprising nature of this discovery that also goes to the nonobviousness of this invention. There is no need to recite the structure of any nucleic acid in the biological sample. The claimed method answers the question of whether a human malarial nucleic acid is present or absent in a sample. Any other nucleic acid in the biological sample (or nucleic acid extracted from the sample) is of no interest. There is no reason to provide any structure for that other nucleic acid.

In view of the foregoing, Applicants respectfully maintain that the invention is properly enabled and described and request the withdrawal of the rejection.

The Rejections under 35 U.S.C. 112, second paragraph

Claims 47, 51 and 56 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention. Applicants respectfully traverse this invention.

Claim 47 is alleged to detect a nucleic acid extracted from the sample. The Patent Office has questioned what nucleic acid is extracted, whether it is bacterial or host cell nucleic acid, and has alleged that "no hybridization agent has been added to the extracted, purified or amplified sample" and that essential reagents and steps are missing from the claims.

Applicants respectfully disagree. It is clear from the language of new claim 50 that the nucleic acid is extracted from the biological sample and that this extracted (etc) nucleic acid is contacted with the probe or primer under conditions allowing hybridization of the probe or primer to nucleic acid of a human plasmodial agent, if present. It should not be necessary to recite the particular hybridization solutions used in the contacting step. After contacting, there is a detecting step, which is dependent on the particular detection molecule or method used. A whole range of such detection systems are well known to the art. See the Specification. Those recited include hybridization with a radioactive or a biotinylated probe (page 20, lines 21-24) or using polymerase chain reaction, restriction fragment length polymorphism, nucleic acid sequence-based amplification, reverse transcriptase polymerase chain reaction, amplification fragment length polymorphism, amplification mismatch detection, interspersed repetitive sequence-polymerase chain reaction (pages 20-26, for discussion). The key aspect of the detection assay which

Applicants provide is the nucleic acid sequence of the hybridizing nucleic acid (probe or primer). With the sequence, one of skilled artisan is readily able to implement a hybridization-dependent assay using methodology well known to the art.

Claim 47 is further alleged to be indefinite in the recitation of alternate embodiments. However, Applicants respectfully submit that the meaning of this claim, and especially of new claim 59, is abundantly clear to one of skill in the relevant art. Claim 47 is replaced by new claim 59. Its language has clarified the source of the nucleic acid and the biological sample and the contacting.

In view of the language of the new language of the new claims, drafted to advance prosecution and believed to readily meet the statutory requirements for clarity, withdrawal of the rejection under Section 112, second paragraph and allowance of the claims is respectfully requested.

The Rejections under 35 U.S.C. 102

Claims 47-56 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Gardner et al. (1993, Nucleic Acids Research). Applicants respectfully traverse this rejection.

New claim 59 specifies that the particular sequence of the probe or primer used in the detection methods, namely, nucleotides 1147-1740 of SEQ ID NO:1 or a probe or primer of at least 15 consecutive nucleotides thereof (or a complementary sequence). In addition, new claim 57 recites that the biological sample is derived from a human or animal which can be infected with a human Plasmodium malarial agent. This language is supported in the as-filed Specification, for example, at page 11, lines 11-12. See also page 12, lines 6-17, where it is clarified that "biological samples may be mosquito or other

vectors of *Plasmodium* ssp., human or animal tissue, blood or derivatives of blood and blood products, amongst others." See also, lines 22-27, where it is stated that the "biological sample may be derived from the blood tissue of a human or animal subject, or cells, nucleic acid molecules and exudates derived therefrom. For example buffy coat, plasma, DNA or RNA, amongst others. The use of dried blood spots derived from human subjects as biological samples for the performance of the assays described herein us particularly contemplated ...".

New claim 59 recites that the biological sample is from a human or animal that can be infected with a human Plasmodium malarial agent. The Gardner reference makes no teaching of a method for detecting Plasmodium organisms in biological samples **from a human or animal** by any hybridization-based assay. The Gardner reference discusses the relatedness of certain sequences across a variety of organisms, including yeast, bacteria, filamentous fungi, algae and plants. In fact, Table 1 on page 1070 of the cited 1993 Gardner reference includes 44 segments of segments of plasmodium sequence, which were conserved in comparison to *E. coli* sequences. The Gardner (1993) reference does not show the use of the particular sequence (nucleotides 1147-1740 or a 15 consecutive-nucleotide probe or primer derived in sequence therefrom) in detection methods. The Gardner reference does not teach the use of the recited sequence or a portion thereof in a hybridization-dependent assay to detect the **presence or absence** of a human malarial agent in a biological sample such as blood or other tissue.

In view of the foregoing discussion and the language of the newly entered claims, Applicants respectfully maintain that the invention as claimed is not anticipated by the cited Gardner reference, and withdrawal of the rejection is requested.

The Rejection under 35 U.S.C. 103(a)

Claims 14-15 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Gardner et al. (1993) in view of Obst et al. (1990). Applicants respectfully traverse this rejection.

The cited Gardner reference is said to teach a method of detecting a human plasmodium malarial agent in a biological sample, by contacting a blood-derived (erythrocyte) sample with a probe or primer that comprises a LSU rRNA nucleic acid sequence of SEQ ID NO:1, nucleotides 1147-1740 that is conserved and found in an extrachromosomal element. Applicants note that the cited reference simply appears to teach that a *P. berghei*-derived sequence hybridizes to *P. b*erghei DNA.

In the interest of advancing prosecution and without acquiescing to the rejection, new claim 59 is drawn to a method for detecting **presence or** absence of a human Plasmodium malarial agent in a biological sample and recites that the biological sample is from a human or animal that can be infected with a human Plasmodium malarial agent. The Gardner reference makes no teaching of a method for detecting Plasmodium organisms in biological samples **from a human or animal** by any hybridization-based assay. The Gardner reference discusses the relatedness of certain sequences across a variety of organisms, including yeast, bacteria, filamentous fungi, algae and plants. In fact, Table 1 on page 1070 of the cited 1993 Gardner reference includes 44 segments of segments of plasmodium sequence, which were conserved in comparison to *E. coli* sequences. The Gardner (1993) reference does not show the use of the particular sequence (nucleotides 1147-1740 or a 15 consecutive-nucleotide probe or primer derived in sequence therefrom) in detection methods. The Gardner reference does not teach the use of the recited sequence or a portion thereof in a hybridization-dependent assay to detect the presence or absence of a human malarial agent in a biological sample such as blood or other tissue.

Applicants have discussed the Gardner (1993) reference above. This reference relates to an analysis of sequence relatedness across a wide variety of organisms, but there appears to be no discussion of the sequence relatedness for the noted sequence among different species of Plasmodium. Applicants emphasize that the cited Garner reference provides no teaching or suggestion that SEQ ID NO:1, nucleotides 1147-1740, or any other plasmodium sequence, is useful in methods for detection of plasmodial species causing malaria in humans in biological samples.

The Obst et al. reference relates to mapping sequences on plant chromosomes and to localizing nuclear sequences in *Plasmodium berghei* in blood smears. Unique nuclear sequences and rRNA probes were used in the experiments described. There is no indication in this reference that the use of probes or primers of the sequences encompassed by those recited in claim 59 would be useful in methods for detection of a Plasmodium in a biological sample, and there is no discussion of the conservation of the recited sequence among Plasmodium species. At most, this reference would provide an invitation to experiment, but there is no teaching or suggestion of the specifically claimed methods nor is there any provision of any reasonable probability of success in the claimed methods, as is required by In re O'Farrell, 7 U.S.P.Q.2d 1673 C.A.F.C, 1988.

Applicants respectfully submit that there is no motivation provided in the cited references for their combination, as required by ACS Hospital Systems, Inc. v. Montfiore Hospital, Inc., 221 U.S.P.Q. 929, C.A.F.C., 1984. See also In re Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988): "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art . . . . Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." . The cited 1993

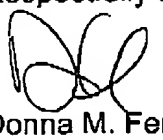
Gardner reference discusses phylogenetic relationships based on a subset of rRNA sequences. The cited Obst reference shows hybridization of a relatively large probe to a slide of *Plasmodium berghei*, but provides no teaching as to the sequence relatedness for other species of Plasmodium. The context appears to be detection of particular sequences but not carrying out a sensitive and reliable method to detect the organism *per se*.

In view of the foregoing discussion and the fact that the cited references provide no reasonable probability of success in the claimed method for the detection or presence of a human malarial agent in a biological sample from a human or animal that can be infected with a human malarial agent, Applicants respectfully state that the invention as claimed is not *prima facie* obvious over the cited references, and the rejection should be withdrawn.

Conclusion

This Amendment is accompanied by a Petition for Extension of Time (one month) and authorization to charge deposit account no. 07-1969 the amount of $120.00 as required by 37 C.F.R. 1.16. It is believed that the present submission does not require the payment of any additional fees under 37 C.F.R. 1.16-1.17. If this is incorrect, please charge any deficiency or credit any overpayment due under the foregoing Rules to Deposit Account No. 07-1969.

Respectfully submitted,



Donna M. Ferber
Reg. No. 33,878

GREENLEE, WINNER AND SULLIVAN, P.C.
4875 Pearl East Circle, Suite 200, Boulder, CO 80301
Telephone (303) 499-8080
Facsimile: (303) 499-8089
Email: winner@greenwin.com
Attorney docket No. 64-99
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